SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of the medicinal product**

Epirubicin Hydrochloride for injection 10 mg

2. **Pharmaceutical Form**

Pharmaceutical Dosage form of the product: Lyophilized Injection

Strength: 10 mg/vial

Route(s) of administration: Intravenous route of administration

3. Qualitative and Quantitative Composition

Epichlor-10
(Epirubicin Hydrochloride for injection 10 mg) Lyophilized

Composition
Each vial contains:
Epirubicin Hydrochloride ..... 10 mg
Methyl Paraben BP ..... 2 mg
Lactose BP ..... qs

4. Clinical Particulars

4.1 Therapeutic indications

Epirubicin HCI injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

4.2 Posology and method of administration

When Epirubicin is used as a single agent, tile recommended dosage in adults is 60-90 mg/m^2 body area; the drug should be Injected I. V. over 3-5 minutes and depending on the patient's haematomedullar status, the dose should be repeated at 21-day intervals. Lower doses (60-75 mg/m^2) are recommended for the patients whose bone marrow function has already been impaired by the previous chemotherapy or radio-therapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2-3 successive days. When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity.

Moderate liver impairment (bilirubin: 1.4-3 mg / 100ml, or BSP retention: 9-15%) requires a 50% reduction of dose while severe impairment (bilirubin>3 mg / l00 ml or BSP rention>15%) necessitates a dose reduction of 75%. Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin excreted by this route.

DIRECTIONS FOR ADMINISTRATION

Epirubicin should be administered by intravenous injection. It is not active when given orally and should not be injected intramuscularly or intrathecally. It is advisable to give the drug via the tubing of a freely running i.v. saline infusion after check that the needle is well placed in the vein. This method minimizes the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Epirubicin rapid dissolution from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Epirubicin rapid dissolution should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drug is in certain proportions. Epirubicin rapid dissolution can be used in combination with other antitumour agents, but is not recommended that it is mixed with these drugs in the same syringe. Epirubicin has also been given by intravesical instillation in the local treatment of bladder cancer. Instillation of 50 mg weekly as a 0.1 % solution (in sodium chloride 0.9% or sterile water) for 8 weeks has been suggested, reduced to 30 mg in 50 ml weekly if chemical cystitis develops; For the prophylaxis of recurrence in patients who have

undergone transurethral resection, 50 mg weekly for 4 weeks, followed by 50 mg instilled once a month for 11 months is the suggested regimen. The solution should be retained in the bladder for 1 hr.

PREPARATION OF INFUSION SOLUTION

Epirubicin 10 mg should be reconstituted to 5ml by adding sterile water for injection BP., and use immediately after preparation.

Epirubicin 50 mg should be reconstituted to 25 ml by adding sterile water for Injection BP., and use immediately after preparation.

Intravenous administration of Epirubicin HCI should be performed with caution. It is recommended that Epirubicin HCI be administered into the tubing of a freely flowing intravenous infusion (0.9% Sodium Chloride or 5% Glucose solution) over a period of 3-5 minutes. This technique is, intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulites, vescication or Tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein (see PRECAUTIONS), beside above regimens, several other protocols has been discussed in different published articles.

4.3 Method of administration

Intravenous Route of Administration

4.4 Contraindications

Patients should not be treated with Epirubicin HCI injection if they have any of the following conditions; Baseline neutrophil count < 1500 cells/mm2 , severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracenediones; or severe hepatic dysfunction.

4.5 Special warning & precautions for use

WARNING.

Epirubicin HCI Injection should be administered only under tile supervision of qualified physicians experienced in the use of cytotoxic therapy. Before beginning treatment with Epirubicin, patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia and generalized infections) of prior cytotoxic treatment. Also, initial treatment with Epirubicin HCI should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin. AST and creatinine and cardiac function as measured by left ventricular ejection function (LVEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression. Supportive care may be necessary for the treatment of severe neutropenia and severe Infectious complications. Monitoring for

potential cardiotoxicily is also important, especially with greater cumulative exposure to Epirubicin.

Severe local tissue necrosis will occur if there is extravasation during administration. Epirubicin must not be given by the intramuscular or subcutaneous route. Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with Epirubicin or months to years after termination therapy.

The probability of developing clinically evident CHF is estimated at approximately 0.9% at a cumulative dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of Epirubicin in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracenediones or concomitant use of other cardio toxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with Epirubicin HCL may occur at lower cumulative doses whether or not cardiac risk factors are present. Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines including Epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Dosage should be reduced in patients with impaired hepatic function. Severe myelosuppression may occur. Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

Hematologic Toxicity A dose dependent reversible leukopenia *and/or* neutropenia is the predominant manifestation of hematologic toxicity associated with Epirubicin and represents the most common acute dose-limiting toxicity of this drug. In most cases, the WBC nadir is reached 10-14 days from drug administration. Leukopenia / neutropenia are usually transient, with WBC and neutrophil counts generally returning to normal values by day 21 after drug administration. As with other cytotoxic agents, Epirubicin HCI at the recommended dose in combination with cyclophosphamide and fluorouracil can produce severe leukopenia and neutropenia. Severe thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, septicemia, septic shock, hemorrhage, tissue hypoxia, symptomatic anemia or death. If myelosuppressive complications occur, appropriate supportive measures (e.g. intravenous antibiotics, colony stimulating factors, transfusions) may be required. Myelosuppression requires careful monitoring. Total and differential white blood cell

(WBC), red blood cell (RBC) and platelet counts should be assessed before and during each cycle of therapy with Epirubicin HCI.

Cardiac Function Cardiotoxicity is a known risk of anthracyclines treatment. Anthracyclines induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of Epirubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as nonspecific ST- T wave changes, but tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia as well as atrioventricular and bundle branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of Epirubicin treatment. Delayed cardiac toxicity results from a characteristic cardiomyopathy that is manifested by reduced LVEF and/or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, hepatomegaly, ascites, pleural effusion, gallop rhythm. Life threatening CHF is the most severe form of anthracycline induced cardiomyopathy. This toxicity appears to be dependent on the cumulative dose of Epirubicin HCI and represents the cumulative dose-limiting toxicity of the drug. if it occurs, delayed cardiotoxicity usually develops late in the course of therapy with Epirubicin HCI or within 2-3 months after completion of treatment but later events (several months to years after treatment termination) have been reported.

Secondary leukemia The occurrence of secondary acute myelogenous leukemia, with or without a preleukemic phase has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of tile anthracyclines have been escalated. These leukemias can have a short 1-3 year latency period.

Liver Function The major route of elimination of Epirubicin is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with Epirubicin HCL. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients. Patients with severe hepatic impairment have not been evaluated; therefore, Epirubicin should not be used in this patient population.

Renal Function Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in Patients with serum creatinine >5 mg/dL. Patients undergoing Dialysis have not been studied.

Tumor-Lysis Syndrome As with other cytotoxic agents. Epirubicin HCI may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug induced rapid lysis of highly chemosensitive neoplastic cells (tumor lysis syndrome). Other metabolic abnormalities may also occur. While not generally a problem in patients

with breast cancer, physicians should consider the potential for tumor-lysis syndrome in potentially susceptible patients and should consider monitoring serum uric acid, potassium, calcium, phosphate and creatinine immediately after initial chemotherapy administration. Hydration, urine alkalinization and prophylaxis with allopurnol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

PRECAUTIONS General Epirubicin HCI Injection is administered by intravenous infusion. Venous sclerosis may result from an injection in to a small vessel or from repeated injections in to the same vein. Extravasation of Epirubicin during the infusion may cause local pain, severe tissue lesions and necrosis. It is recommended that Epirubicin HCI be slowly administered in to the tubing of a freely running intravenous infusion. If possible, veins over joints or in extremities with compromised venous or lymphatic drainage should be avoided. The dose should be administered over 3-5 minutes. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur without causing pain. Facial flushing, as well as local erythematous streaking along the vein, may be indicative of excessively rapid administration. It may precede local phlebitis or thrombo phlebitis.
Patients administered the 120 mg/m^2 regimen of Epirubicin HCI as a component of combination chemotherapy should also receive prophylactic antibiotic therapy with trimethoprim sulfamethoxazole. Administration of Epirubicin by intravesical route may produce symptoms of chemical cystitis.

4.6 Interaction with other medicinal products and other forms of interactions

No specific drug interaction study of Epirubicin hydrochloride has been conducted.

4.7 Pregnancy and lactation

Epirubicin HCI may cause fetal harm when administered to a pregnant woman. Administration of 0.8 mg /kg/day intravenously of Epirubicin to rats (About 0.04 times the maximum recommended single human dose on body surface area basis) during days 5-15 of gestation was embryotoxic (Increased resorptions and post implantation loss) and caused fetal growth retardation (decreased body weight) but was not teratogenic up to this dose. Administration 2 mg/kg/day Intravenously of Epirubicin to rats (about 0.1 times the maximum recommended single human dose on a body surface area basis) on days 9 and 10 of gestation was embryotoxic (increased late resorptions. Post implantations losses and dead fetuses and decreased live fetuses) retarded fetal growth (decreased body weight) and caused decreased placental weight. This dose was also teratogenic. causing numerous external (anal tresia. misshapen tail, abnormal genital

tubercle) visceral (primarily gastrointestinal. urinary and cardiovascular systems) and skeletal (deformed long bones and gridles, rib abnormalities, irregular spinal ossification) malformations. Administration of intravenous Epirubicin to rabbits at dose up to 0.2 mg/kg/day (about 0.02 times the maximum recommended single human dose on a body surface area basis) during days 6 to18 of gestation was not embryotoxic, but maternally toxic dose of 0.32 mg/kg/day increased abortion and delayed ossification. Administration of a maternally toxic Intravenous dose of 1 mg/kg/day Epirubicin to rabbits (about 0,1 times the maximum recommended single human dose on a body surface area basis) on days 10-12 of gestation induced abortion, but no other signs of embryo fetal toxicity or teratogenicity were observed. When dose up to 0.5 mg/kg/day Epirubicin were administered to rat dams from day 17 of gestation to day 21 after delivery (About 0.025 times the maximum recommended single human dose on a body surface area basis) no permanent changes were observed in the development, functional activity, behavior, or reproductive performance of the offspring. There are no adequate and well-controlled studies in pregnant women.

NURSING MOTHERS Epirubicin was excreted into milk of rats. It is not known whether Epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential or serious adverse reactions in nursing infants from Epirubicin, mothers should discontinue nursing prior to taking this drug.

4.8 Effects on ability to drive and use machine

Not known.

4.9 Undesirable effects

Apart from myelosuppression and cardiotoxicity (described under precautions the following adverse reactions have been described).

-- Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by the lack of beard growth in males;

-- Mucositis may appear 5-10 days after the start of treatment and usually involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa;

-- Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea;

-- Hyperpyrexia.

4.10 Overdose

The observed adverse events due to over dosage were qualitatively similarly to known toxicities of Epirubicin. Most of the patients recovered with appropriate supportive care. If an over dosage occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors and intensive care as needed) should be provided until the recovery of toxicities. Delayed CHF has been observed months after anthracycline administration. Patients must be observed carefully over time for signs of CHF and provided with appropriate supportive therapy.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic drug

ATC Code: L01DB03.

Epirubicin is an anthracycline cytotoxic agent and forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA & RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity preventing the enzymatic separation of double - stranded DNA & interfering with replication and transcription. Epirubicin is also involved in oxidation / reduction reactions by generating cytotoxic free radicals.

In patients with normal hepatic and renal function, plasma levels after i.v injection of 75-90 mg/m^2 of the drug follow a tri-expontential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13-0H derivative, are constantly lower and virtually parallel to those of the unchanged drug. Epirubicin is eliminated mainly through the liver, high plasma clearance values (0.9 l/min.) indicate that this slow elimination is due to extensive tissue distribution. The drug does not cross the blood-brain barrier.

5.2 Pharmacokinetic Properties

Epirubicin pharmacokinetics is linear over the dose range of 60 -150 mg/m^2 and plasma clearance is not affected by the duration of infusion or administration schedule. Pharmacokinetic parameters for epirubicin following 6-10 minutes, single dose intravenous infusions of epirubicin at doses of 60-150 mg/m^2 in patients with solid tumors are shown in TABLE 1. The plasma concentration declined in triphasic manner with mean half-lives for the alpha, beta & gamma phases of about 3 minutes, 2.5 hrs and 33 hours respectively.

TABLE: Summary of mean (±SD) Pharmacokinetic Parameters in Patients' with Solid Tumors Receiving Intravenous Epirubicin 60 to 150 mg/m^2

Dose[2] (mg/m^2)	C_{max} ($ug.h/m^2$)	AUC[4] ($ug.h/m^2$)	t ½[5] (h)	CL[6] (L/h)	Vss[7](L/kg)
60	5.7± 1.6	1.6± 0.2	35.3± 9	65 ± 8	21 ± 2
75	5.3± 1.5	1.7± 0.3	32.1± 5	83 ± 14	27 ± 11
120	9.0± 3.5	3.4± 0.7	33.7± 4	65 ± 13	23 ± 7
150	9.3± 2.9	4.2± 0.8	31.1± 6	69 ± 13	21 ± 7

1) Advanced solid tumor cancers, primarily of the lung.
2) N = 6 patients per dose level.
3) Plasma concentration at the end of 6-1 0 minute infusion.
4) Area Under the plasma concentration curve.
5) Half-life of terminal phase.
6) Plasma clearance.
7) Steady state volume of distribution.

5.3 Preclinical safety data

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6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose BP
Methyl Hydroxybenzoate BP
Sodium Hydroxide BP
Water for Injection BP

6.2 Incompatibilities

None

6.3 Shelf life

The shelf life of the medicinal product as package for sale
36 Months

The shelf life after dilution or reconstitution according to directions
Not Applicable.

The shelf life after first opening the container
Not Applicable

6.4 Special precaution for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

UNIT PACK: 5 ml flint tubular Type I glass vial closed with 20 mm grey bromo butyl rubber stopper and sealed with red flip-off aluminium seals, packed in a printed carton with pack insert.

7. Marketing Authorization Holder and Manufacturing site address

Name of Marketing Authorization Holder:
Khandelwal Laboratories Pvt. Ltd.

Address of manufacturing site:
B-1, Wagle Industrial Estate,
Thane - 400 604, India
Telephone: 00 91 22 25821793 / 0794
Fax: 00 91 22 25823837

8. Marketing Authorization Numbers

06317/06770/NMR/2018

9. Date of first authorization / renewal of the authorization

Jul 25, 2021

10. Date of revision of the text

Jul 25, 2021